ANTIARRHYTHMIC POTENCY OF N-PROPYL AJMALINE
WITH UNTOWARD RESPONSE OF VENTRICULAR
FIBRILLATION IN EXCESS DOSE

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Abstract—The antiarrhythmic activities of N-propyl ajmaline was evaluated in
anesthetized dogs. N-propyl ajmaline was effective on aconitine-induced atrial and
ouabain-induced ventricular arrhythmias. Antiarrhythmic activity of N-propyl ajmaline
was ten times more potent than that of ajmaline. Rapid infusion of N-propyl ajma-
iline induced ventricular flutter and fibrillation, but these effects were abolished by
pre-treatment with β-adrenergic blocking agent.

Concerning N-(n-propyl) ajmaline bromide or bitartrate, a water soluble derivative
of ajmaline, several reports have been published on the toxicity and antiarrhythmic effect
on either experimental or clinical arrhythmias. Gendenshtein (1, 2) demonstrated that
the mode of antiarrhythmic effect of N-propyl ajmaline bromide for auricular and ventri-
cular arrhythmias induced either by electrical stimulation, or by drugs such as aconitine,
acetylcholine, ouabain and calcium chloride in rats and dogs was similar to that of ajma-
line but was Approx. ten times more effective and four to eight times more toxic in mice
and guinea-pigs. Philipsborn (3), Weidner and Philipsborn (4) reported that bitartrate of
N-propyl ajmaline was five to six times more effective on aconitine-induced arrhythmia
in rats but five or six times more toxic than ajmaline.

In previous papers the authors suggested that ajmaline would be a most authentic
antiarrhythmic compound as almost the same effective dose was obtained for different
kinds of experimental arrhythmia and by different procedures of administration (5, 6).

In this study antiarrhythmic activities of N-propyl ajmaline bitartrate were evaluated
on aconitine-induced atrial and ouabain-induced ventricular arrhythmias in dogs.

METHODS

Experiments were performed on mongrel dogs of both sexes weighing 9 to 15 kg. Ani-
mals were anesthetized with pentobarbital sodium, 30 mg/kg i.v. In order to induce atrial
arrhythmia, a cup method was used which was developed by the authors instead of the

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cotton pledget (7) for application of aconitine solution on a very restricted area of atrium (5). The cup which adhered on the surface of the right atrium was filled with one percent of aconitine solution. Within a few minutes a sustaining arrhythmia was induced without any irreversible disorder in the cardiac function for several hr.

For inducing ouabain arrhythmia, ouabain was given i.v. as follows: An initial dose of 40 μg/kg was followed by 20 μg/kg after 30 min and an additional dose of 10 μg/kg was

![Graph](image)

**FIG. 1.** Suppression of aconitine-induced atrial arrhythmia by N-propyl ajmaline given by the titration procedure. HR, heart rate; SBP, systemic blood pressure and ECG (lead II).

**TABLE 1.** Effect of N-propyl ajmaline and ajmaline on aconitine-induced atrial arrhythmia given by the titration procedure. Drugs were infused until the following three effects had been attained: 1) complete recovery of A-V conduction, 2) reduction of heart rate below 200 beat per min, 3) disappearance of sinus arrhythmia. a) HR, heart rate; b) SBP, systolic blood pressure at the femoral artery; c) DBP, diastolic blood pressure at the femoral artery; d) NS, statistically not significant difference from control, e) Data were reported previously by the present authors in Europ. J. Pharmacol. 14, 9 (1971). Values represent mean ± S.E.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>No. of exp.</th>
<th>Before aconitine treatment</th>
<th>No. of effective cases</th>
<th>Effective dose (mg/kg)</th>
<th>At the effective dose</th>
<th>Duration (min)</th>
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<tbody>
<tr>
<td></td>
<td>HR a)</td>
<td>SBP b)</td>
<td>DBP c)</td>
<td></td>
<td>HR</td>
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<tr>
<td>N-propyl ajmaline bitartrate</td>
<td>5</td>
<td>182 ± 7</td>
<td>127 ± 4</td>
<td>90 ± 4</td>
<td>0.25 ± 0.02</td>
<td>177 ± 15</td>
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<td>113 ± 7</td>
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<td></td>
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<td>NS d)</td>
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<tr>
<td>Ajmaline c)</td>
<td>8</td>
<td>160 ± 6</td>
<td>154 ± 8</td>
<td>99 ± 11</td>
<td>3.2 ± 0.8</td>
<td>167 ± 6</td>
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<td>122 ± 13</td>
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<td>NS d)</td>
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<td>65 ± 12</td>
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<td>17 ± 3</td>
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ANTIARRHYTHMIC EFFECT OF N-PROPYL AJMALINE

given at 15 min intervals until ventricular arrhythmia developed. Supramaximal electrical stimulation of the right vagal nerve did not affect the arrhythmia when it was fully developed (8).

Test compounds were infused intravenously. Infusion was interrupted when the normal sinus rhythm was restored and the duration of antiarrhythmic activity was determined. Criteria of antiarrhythmic activity has been previously described (5, 6). Student's t-test was carried out for statistical analysis of the results.

Fig. 2. Suppression of ouabain-induced ventricular arrhythmia by N-propyl ajmaline given by the titration procedure. The upper diagram shows the process of induction of ventricular arrhythmia by ouabain and successful suppression by N-propyl ajmaline at the lower rate of infusion of 0.02 mg/kg/min. The shaded column indicates arrhythmic heart rate. The records at a, b, c, d, e and f in the upper diagram are illustrated. SBP, the phasic change of systemic blood pressure and ECG (lead II).
RESULTS

Intravenous infusion of N-propyl ajmaline at a rate of 0.02 mg/kg/min converted aconitine-induced atrial arrhythmia into regular sinus rhythm and heart rate was reduced below 200 with recovery of 1:1 rhythm. The effective dose of N-propyl ajmaline for conversion into normal sinus rhythm was 0.25 ± 0.02 mg/kg i.v. (mean ± S.E.). Antiarrhythmic potency of N-propyl ajmaline was more than 10 times effective in comparison with ajmaline, while the duration of antiarrhythmic action was approx. the same (Fig. 1 and Table 1). Effective dose of N-propyl ajmaline caused no significant change in heart rate and systolic and diastolic blood pressure at the femoral artery (Table 1). On the other hand rapid intravenous infusion of N-propyl ajmaline at a rate of 0.5 mg/kg/min which was adopted in the evaluation of antiarrhythmic activity of ajmaline (5, 6) caused severe hypotension and ventricular arrhythmias in five dogs. Single ectopic beat occurred initially and within a short time the number of ectopic beats increased with flutter and fibrillation eventually evident. Ventricular flutter or ventricular fibrillation was at onset 1.8 ± 0.6 mg/kg i.v. (mean ± S.E.) in five dogs (Table 3).

Ventricular arrhythmia produced by ouabain was effectively abolished and the vagal stimulation induced again sinus bradycardia in all five dogs by intravenous infusion of N-propyl ajmaline at a rate of 0.02 mg/kg/min. A typical record is illustrated in Fig. 2. The effective dose of N-propyl ajmaline was 0.34 ± 0.13 mg/kg i.v. (mean ± S.E.), which did not produce any significant hemodynamic change. N-propyl ajmaline was ten times more potent than that of ajmaline (Table 2). Rapid infusion of N-propyl ajmaline (0.5 mg/kg i.v.), however, augmented the severity of arrhythmia. Ventricular flutter or fibrillation occurred in five dogs as shown in Fig. 3, while in one animal intermittent ventricular

<table>
<thead>
<tr>
<th>Drugs</th>
<th>No. of exp.</th>
<th>Before ouabain treatment</th>
<th>No. of effective cases</th>
<th>Effective dose (mg/kg)</th>
<th>At the effective dose (min)</th>
<th>Duration (min)</th>
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<td>N-propyl ajmaline bitartrate</td>
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<td>164±20</td>
<td>175±11</td>
<td>0.34±0.13</td>
<td>158±10</td>
<td>40±14</td>
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<td></td>
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<td>125±9</td>
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<td>124±3</td>
<td>NS d)</td>
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<tr>
<td>Ajmaline e)</td>
<td>7</td>
<td>168±12</td>
<td>179±14</td>
<td>4.5±1.4</td>
<td>119±10</td>
<td>193±25</td>
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<td></td>
<td></td>
<td></td>
<td>113±10</td>
<td></td>
<td>p&lt;0.05</td>
<td>90 f)</td>
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Table 2. Summarized data of antiarrhythmic effects on ouabain-induced ventricular arrhythmia. A) HR, heart rate; b) SBP, systolic blood pressure at the femoral artery; c) DBP, diastolic blood pressure at the femoral artery; d) NS, statistically not significant difference from control; e) Data were reported previously by the present authors in Experientia 27, 666 (1971); f) After i.v. administration of 10 mg/kg; g) Statistically different from control (p<0.05).
flutter occurred initially and then sudden cardiac arrest (Table 3). Prior treatment with β-adrenergic blocking agent CS-359 (5-methyl-8 (2-hydroxy-3-t-butylaminopropoxy) coumarin hydrochloride (9, 10) fully abolished the incidents of ventricular flutter or fibrillation produced by rapid infusion of N-propyl ajmaline in four dogs (Table 3). Typical data is illustrated in Fig. 4.

**DISCUSSION**

The present studies with N-propyl ajmaline, a derivative of ajmaline, have shown antiarrhythmic properties against cardiac arrhythmia induced by either aconitine or oua-
TABLE 3. Effect of N-propyl ajmaline on aconitine-induced atrial and ouabain-induced ventricular arrhythmias given by infusion at a higher rate of 0.5 mg/kg/min. Preventive effect of a β-adrenergic blocking agent CS-359 on arrhythmogenic action of N-propyl ajmaline in ouabain-induced ventricular arrhythmia. Values represent means ± S.E.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose or treatment</th>
<th>Type of arrhythmia</th>
<th>No. of exp.</th>
<th>Dose at onset of normal sinus rhythm (mg/kg)</th>
<th>Dose at onset of ventricular flutter or fibrillation (mg/kg)</th>
<th>Dose at onset of ventricular asystole (mg/kg)</th>
<th>No. of cases</th>
<th>No. of cases</th>
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<tr>
<td>Aconitine-induced atrial arrhythmia</td>
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<td>1.8 ± 0.6</td>
<td>5</td>
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<tr>
<td>N-propyl ajmaline 0.5 mg/kg/min</td>
<td>Ouabain-induced ventricular arrhythmia</td>
<td>6</td>
<td>2.0 ± 0.3</td>
<td>0.4</td>
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<td>CS-359 + N-propyl ajmaline Pretreatment</td>
<td>Ouabain-induced ventricular arrhythmia</td>
<td>4</td>
<td>2.0 ± 0.2</td>
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FIG. 4. Successful prevention of arrhythmogenic action of N-propyl ajmaline by prior treatment with β-blocking agent CS-359 (5-methyl-8(2-hydroxy-3-t-butylaminopropoxy) coumarin hydrochloride. Explanation of the figure is the same as in Fig. 2.
bain. Weidner and Philipsborn found that a dose of 0.2 mg/kg N-propyl ajmaline was equivalent to 1.0 mg/kg ajmaline in antiarrhythmic activity and also in toxic effect (4). Kadatz and Rossbach reported that N-propyl ajmaline was much more effective than ajmaline in prolonging the effective refractory period in isolated guinea-pig atria (11). Heistracher and Pillat (12, 13) observed that N-propyl ajmaline and quinidine had essentially the same effect in cardiac muscle fibers of calves and sheep and that the relative refractory period was prolonged; the amplitude and the rate of rise of action potential was markedly decreased; conduction was slowed and the threshold for electrical excitation was elevated. Heistracher et al. suggested that N-propyl ajmaline and other antifibrillatory drugs depressed the sodium permeability in cardiac muscle fibers of mammalian heart (14, 15).

Although the mode of action of N-propyl ajmaline is similar to that of other antiarrhythmic compounds, an effective dose of N-propyl ajmaline is much smaller than any other antiarrhythmic drugs. Szekers and Szomolensky observed that higher doses of the antiarrhythmic drugs sometimes showed an augmentation of severity of arrhythmia and caused ventricular fibrillation instead of a normalization of rhythm (16). Induction of ventricular arrhythmia by antiarrhythmic drugs can probably be ascribed to the depression of atrioventricular conduction which represents one factor of toxic effects. Rapid infusion of N-propyl ajmaline induced ventricular flutter or fibrillation which was effectively depressed by a prior administration of β-adrenergic blocking agents. Bertaccini et al. also observed that combined use of antiarrhythmic drugs and β-adrenergic blocking agents tended to reduce the sum of the single negative inotropic and chronotropic effects (17).

In the present studies, however, it was not clear whether the curative effect of combined use of N-propyl ajmaline and β-adrenergic blocking agent was additive or synergistic. Since arrhythmogenic action of N-propyl ajmaline was abolished with a small amount of β-adrenergic blocking agent, β-adrenergic mechanism may participate in augmentation of severity of arrhythmias. In these experiments, a high level of heart rate was evident (Tables 1 and 2) which indicates the high sympathetic tone caused by pentobarbital anesthesia.

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